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Treatment as Prevention and Other Interventions to Decrease MDR-TB Transmission

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Summary

Drug resistant tuberculosis (DR-TB) represents a major programmatic challenge at the national and global level. Only ~30% of patients with multidrug-resistant (MDR) TB were diagnosed and ~25% were initiated on therapy for MDR-TB in 2016. Increasing evidence now points towards primary transmission of DR-TB rather than inadequate treatment as the major driver of the DR-TB epidemic. The cornerstone of DR-TB transmission prevention should be earlier diagnosis and prompt initiation of effective treatment for all patients with DR-TB. Despite the extensive scale up of Xpert MTB/RIF testing, major implementation barriers continue to limit its impact. Although there is longstanding evidence in support of the rapid impact of treatment on patient infectiousness, delays in the initiation of effective DR-TB treatment persist, resulting in ongoing transmission. However, it is also imperative to address the burden of latent DR-TB infection, since it is estimated that many DR-TB patients will become infectious prior to seeking care and encounter various diagnostic delays before treatment. Addressing latent DR-TB primarily consists of identifying, treating and following contacts of patients with MDR-TB, typically through household contact evaluation. Adjunctive measures such as improved ventilation and use of germicidal ultraviolet (GUV) technology can further decrease TB transmission in high-risk congregate settings. Although many gaps remain in our biological understanding of TB transmission, implementation barriers to early diagnosis and rapid initiation of effective DR-TB treatment can and must be overcome if we are to impact DR-TB incidence in the short and long-term.

Keywords

tuberculosis; MDR; transmission; active case finding

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Background

Drug resistant tuberculosis (DR-TB) represents a major programmatic challenge at the national and global level and a serious danger to people living in TB endemic countries. The World Health Organization (WHO) reported that of the 490 000 people estimated to have developed multidrug-resistant TB (MDR-TB) in 2016 (with an additional 110 000 cases of rifampicin [RMP]-resistant TB), only ~30% were diagnosed and ~25% were initiated on treatment for MDR-TB¹.

For decades, it was thought that DR-TB strains were relatively less transmissible than drug susceptible strains, which drove global policy to focus on the management of drug susceptible TB (DS-TB). Experiments using animal models in the 1950s demonstrated that some DR-TB (predominantly isoniazid-[INH] resistant) strains were less pathogenic than DS-TB strains^{2, 3}. However, although drug resistance mutations can impair fitness in laboratory settings, clinical strains that cause disease (by definition) have to be virulent and may have undergone compensatory mutations that restore fitness⁴.

Various modeling studies have demonstrated heterogeneity in the fitness of DR-TB strains, highlighting that even a small number of relatively fit DR-TB strains can outcompete DS-TB and less fit DR-TB strains^{5, 6}. Epidemiological studies have shown conflicting results with some demonstrating a 50% reduction in transmission of MDR-TB to household contacts compared to DS-TB⁷. However, other household contact studies demonstrated high rates of TB disease and infection if index patients had DR-TB strains^{8–10}. Global TB policy guidance now recommends early diagnosis, including assessment for drug resistance, and prompt, effective treatment for all patients with TB¹¹.

Until recently, DR-TB transmission prevention efforts have focused primarily on decreasing acquisition of drug resistance due to poor adherence to first line TB treatment. However, increasing evidence now points towards primary transmission of DR-TB rather than inadequate treatment as the main driver of the DR-TB epidemic. Genotypic analyses from a large study in KwaZulu-Natal, South Africa, evaluating extensively drug-resistant (XDR) TB demonstrated that 69% of patients with XDR-TB had never received prior treatment for MDR-TB¹². Cluster analyses showed that 30% had identifiable evidence of person-to-person and hospital-based transmission, although known epidemiological links were not established for the majority of transmitted cases. A large epidemiological study from Shanghai, China, which, in contrast to KwaZulu-Natal, is a low HIV prevalence setting, reported that 70% of MDR-TB cases arose from transmission¹³. Less easily measured is the number of previously treated patients who become re-infected with MDR-TB, including those who are re-infected with the same circulating MDR-TB strain (often misclassified as 'reactivation', thus underestimating transmission estimates). Exogenous reinfection may account for as much as 60% of recurrent TB¹⁴. The high proportion of undiagnosed patients with MDR-TB is likely to be a major driver of TB transmission and also limits understanding of where and how transmission occurs since these patients are not included in analyses.

Here, we focus on the role of prompt and effective treatment as the most important tenet of MDR-TB transmission prevention. We do so by addressing the approach to treatment in

several categories: the scientific basis for early diagnosis and treatment of active MDR-TB disease as a transmission prevention approach (including the probable role of surgery); preventive therapy for MDR-TB for household contacts and others with known exposure to MDR-TB; active or enhanced case finding interventions focused on congregate settings; the neglected management of patients with refractory or incurable DR-TB to prevent transmission; and other adjunctive interventions to decrease transmission.

Early diagnosis and initiation of effective treatment for all patients with drug-resistant TB

As is the case for TB transmission prevention overall, the cornerstone of MDR-TB transmission prevention should focus on earlier diagnosis and prompt initiation of effective therapy for all patients with DR-TB, since transmission is driven by patients with unsuspected DR-TB (this includes patients on treatment for DS-TB who have undiagnosed DR-TB as well as those who remain both undiagnosed and untreated)¹⁵. This strategy will improve individual outcomes and decrease transmission by rendering these patients non-infectious. The WHO's End TB Strategy, launched in 2015, sets out an ambitious agenda to achieve its targets, which includes a 90% reduction in TB incidence¹¹. The End TB Strategy calls for universal drug susceptibility testing (DST) for all persons being evaluated for TB, and not only those with known risk factors for DR-TB disease. This strategy requires massive scale-up of implementation of molecular diagnostics for TB that enable an initial assessment for drug resistance at the time of TB diagnosis.

Although WHO recommends Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) as the initial test for all persons being evaluated for TB¹⁶, only 15 of the 29 high TB incidence countries currently recommend Xpert for this use¹⁷. Scale up of Xpert has been hindered by high costs, weak infrastructure and inadequate implementation plans that include quality assurance and maintenance support¹⁸. A large multicenter cohort study conducted in 18 countries reported that only 4% of patients with HIV-TB co-infection had undergone Xpert testing¹⁹. Additionally, if Xpert reveals evidence of rifampicin resistance, prompt second-line DST should be initiated to prevent ongoing transmission from undetected XDR-TB. A study from South Africa demonstrated that only 44% of 1332 patients with rifampicin-resistant TB had second-line DST for both fluoroquinolones (FQs) and second-line injectable agents²⁰.

Other existing diagnostic assays, which include an assessment for drug resistance such as line probe assays (LPA)²¹ or the microscopic observation of drug susceptibility (MODS) assay,²² require significant technical expertise and laboratory infrastructure, which limit their impact as initial diagnostic tests. Xie et al. recently published promising results for a new automated cartridge-based molecular TB assay that detected resistance to FQs, aminoglycosides and INH directly from sputum specimens (83% sensitivity for INH, 88%–92% sensitivity for moxifloxacin depending on the critical concentration used, 71% sensitivity for kanamycin and 71% sensitivity for amikacin, with an average specificity of 94%)²³. These sensitivities all increased to >90% and specificity rose to 99% when DNA sequencing rather than phenotypic DST was used as the reference standard. Further work is in progress to develop this assay.

There is interest in the potential for whole genome sequencing (WGS) to enable the rapid delivery of 'personalized' DR-TB regimens and improved investigation of transmission events in outbreak scenarios. A study which implemented a WGS-based diagnostic system in eight laboratories in Europe and North America reported that full WGS results could be generated in a median of 9 days versus 31 days for final reference laboratory results at a lower cost²⁴. One case of MDR-TB and a new cluster of MDR-TB was diagnosed through WGS prior to the completion of the routine diagnostic workflow, enabling treatment to be initiated more rapidly. However sequencing was performed on newly positive liquid cultures, which are not routinely obtained in most high DR-TB incidence settings due to resource and infrastructure limitations. Public Health England is the first program to perform WGS on all strains isolated in routine clinical practice in the United Kingdom but the impact on individual and programmatic care is unknown.

Data on the impact of TB treatment on infectiousness are primarily derived from studies using the human-to-guinea-pig model, established by Richard Riley and colleagues in the late 1950s, which demonstrate that transmission is stopped by effective treatment^{25, 26}. More recently, using a human-to-guinea-pig model in South Africa, Dharmadhikari et al. showed that only 1% of guinea pigs (1/90) developed TB after being exposed to patients with MDR-TB who were on effective treatment over a three-month period, and that transmission occurred from patients with unsuspected XDR-TB²⁷.

As stated above, MDR-TB incidence is primarily driven by transmission from patients with undiagnosed and untreated (or ineffectively treated) MDR-TB. A 2007 study from Russia demonstrated that patients who had any part of their TB treatment in hospital had a substantially higher risk of developing MDR-TB than equally adherent patients treated on an ambulatory basis (hazard ratio 6.3)²⁸. During the months that it took to observe treatment failure on treatment for DS-TB, patients with unsuspected MDR-TB transmitted their infection, thereby re-infecting patients with DS-TB. More recently, Xpert testing was applied to all new TB admissions to two TB hospitals in Russia¹⁵. Those testing positive were treated for MDR-TB within just a few days. Compared to historical control cohorts in the same hospital, there was a 78% odds reduction in the risk of developing MDR-TB. These data support the hypothesis that by reducing the period of exposure to untreated MDR-TB, MDR-TB incidence will fall.

A recent study using a transmission model based on data from Vietnam indicated that if all identified patients with active TB, who had been treated previously, underwent DST, and 85% of those diagnosed with MDR-TB initiated treatment, based on current MDR-TB treatment success rates, MDR-TB incidence in 2025 could be reduced by 26% (95% uncertainty range [UR] 4–52%) due to the impact of effective treatment on transmission²⁹. The authors went on to model a scenario in which all patients with active TB diagnosed with MDR-TB received a novel treatment regimen with similar effectiveness and tolerability as current treatment for DS-TB, and showed that MDR-TB incidence could be reduced by 54% (95% UR 20–74%) by 2025.

Increasing evidence, primarily from observational cohort studies, suggests that regimens that include new drugs such as bedaquiline (BDQ) and delamanid (DLM) or repurposed drugs

such as linezolid and clofazimine can improve DR-TB outcomes, including culture conversion, treatment success and mortality^{30–32}. However, some observational cohort data have demonstrated high rates of reversion of culture conversion in patients with FQ-resistant TB, suggesting that longer durations (more than 6 months) of BDQ may be required for patients with more resistant disease³³. Interim data from the EndTB phase III clinical trial have shown that 79% of the 658 patients included in the DLM analysis achieved culture conversion, and safety analyses did not demonstrate any major safety issue with either BDQ or DLM. Data from the arms of the randomized controlled STREAM (Short-course treatment for multidrug-resistant TB) trial, which include BDQ-containing regimens, are eagerly awaited³⁴.

Surgery to reduce drug-resistant TB transmission

Patients with localized pulmonary DR-TB that is refractory to chemotherapy and marked by persistent smear and culture positivity represent a transmission risk. These patients often have extensive pulmonary disease, with cavitary lesions and areas of scarring³⁵. Anti-TB drugs have variable sterilizing activity in pulmonary cavitary lesions, which may create conditions for the amplification of drug resistance, unrestricted bacterial growth and generation of infectious aerosols containing DR-TB strains³⁶.

Surgery has been used as an adjunct to chemotherapy to manage patients with DR-TB who have a high risk of failure or relapse, often due to smear positivity and/or cavitary disease, particularly in those with XDR-TB. Candidates for surgery typically have unilateral disease (although some with apical bilateral disease may be considered) and adequate pulmonary reserve¹⁶.

The goal of the surgical procedure is removal of infected and devitalized pulmonary parenchyma, with the extent of resection (pneumonectomy, segmentectomy, lobectomy, wedge resection) depending on disease extent. Excision of cavities has been hypothesized to decrease the overall mycobacterial burden, but also to remove areas with a high concentration of DR-TB bacilli, thereby enhancing the response to postoperative chemotherapy^{37, 38}.

It has been reported that resection reduces infectiousness, as evidenced by sustained conversion of persistently positive smear and culture to negative^{39–41}. Meta-analysis based on observational data have also demonstrated improved outcomes for patients with DR-TB, particularly XDR-TB, who received surgical intervention compared to medical treatment alone^{42, 43}. Several questions, such as the optimal timing for surgery, duration of pre- and postoperative chemotherapy and use of adjunctive investigations such as positron emission tomography-computed tomography (PET/CT) remain⁴⁴. Nonetheless, surgical centers with the requisite expertise to perform these surgical procedures are scarce and often inaccessible. Surgery for DR-TB also presents its own risk of transmission in the operating room and recovery area⁴⁵.

Treatment of latent multidrug-resistant TB infection

Although household transmission may only account for between 8% and 19% of the overall proportion of TB transmission in high TB and HIV incidence settings⁴⁶, reducing TB

transmission within the household continues to represent an important (and more easily actionable) focus for TB transmission prevention efforts, which is emphasized in low-incidence settings. Once an index patient has been diagnosed with TB, at a minimum, all household contacts should be screened for active TB disease, given the high yield of active case finding among household contacts⁹. This is particularly relevant for decreasing MDR-TB transmission because 75% of people estimated to have MDR-TB are not diagnosed¹ and those who are diagnosed often experience diagnostic delays⁴⁷. There is a strong evidence base for the treatment of latent DS-TB;⁴⁸ however, evidence to inform recommendations for preventive MDR-TB therapy is limited.

Although there is a lack of data from randomized clinical trials, the WHO updated its latent TB guidelines in 2018 to state that preventive therapy (regimen to be based on source DST) for selected high-risk contacts (children, people on immunosuppressive therapy or people with HIV) of patients with MDR-TB may be considered, based on individualized risk assessment and sound clinical justification⁴⁹. The WHO recommendation also states that strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required regardless of the provision of preventive therapy. Similarly, a consensus paper issued by a group of experts in 2015 recommended considering FQ preventive therapy in high-risk contacts (at least child contacts aged <5 years and immunocompromised persons of any age) with either levofloxacin (LVX) if the source patient's DST confirmed FQ susceptibility or if background FQ resistance was low, or moxifloxacin if DST confirmed ofloxacin resistance or background FQ resistance was high⁵⁰. This expert group also considered concurrent treatment with INH to treat co-infection with a DS-TB strain and for adjunctive therapy against MDR-TB strains if given at a high dose. A systematic review by Marks et al. in 2017 found that, despite limited data (6 studies comparing outcomes for persons treated and untreated for latent MDR-TB infection), there was a reduced risk of TB incidence with treatment of latent MDR-TB infection. Treatment discontinuation rates were high with pyrazinamide-containing regimens. Although the most effective regimen was FQ, combined with ethionamide, this regimen was more expensive than others and not considered cost-effective. FQ and ethambutol was the most effective, followed by FQ alone, then by pyrazinamide and ethambutol⁵¹.

Three randomized controlled trials that evaluate different regimens for MDR-TB preventive therapy are underway, although results are not anticipated until at least 2020⁵². The TB-CHAMP (Tuberculosis child multidrug-resistant preventive therapy) study, based in South Africa, will evaluate six months of LVX vs. placebo in children aged <5 years, with a planned 18-month follow-up period. The V-QUIN study being undertaken in Vietnam will evaluate six months of LVX vs. placebo in all contacts (adults and children) with a planned 30-month follow-up period. The PHOENix trial is a multi-site study at various household contact study sites across Africa, South America and Asia, and will compare six months of DLM vs. standard-dose INH with a planned 22-month follow-up period. It is unclear whether these trials have attempted to standardize their subgroup eligibility criteria and analysis plans to facilitate evaluation of trial results to inform future guideline development.

Both this expert group and others have emphasized that the alternative to not providing preventive therapy cannot be inaction⁵². Implementation of the periodic screening of MDR-

TB contacts for 2 years (as recommended by the WHO) is inadequate and unmeasured, and has led to calls for national TB programs to maintain a registry of MDR-TB contacts that records interventions and 24-month outcomes⁵². This approach would provide valuable observational programmatic data to be evaluated alongside trial data.

Active case finding for high-risk groups and congregate settings

Efforts to scale-up treatment for active DR-TB disease and DR-TB infection in high incidence settings should be accompanied by efforts to characterize and address community transmission risks. Molecular epidemiological studies have demonstrated high rates of transmission in crowded congregate settings, including healthcare facilities⁵³, shelters⁵⁴, mines and prisons⁵⁵. However, the limitations of these studies include being undertaken during outbreaks in which the source cases may not be identified with certainty, and variability in patient infectiousness and the latency period. Frequent low-intensity exposures may be responsible for a greater proportion of transmission than fewer high-intensity exposures^{56, 57}.

TB transmission in healthcare facilities is thought to be primarily driven by patients with unsuspected (and thus untreated TB) because TB infection control (TB-IC), if implemented, focuses on patients with known and suspected TB. However, in many settings without access to rapid DST, patients with unsuspected DR-TB may be on ineffective treatment (for presumed DS-TB) and contribute to ongoing transmission⁵⁸.

FAST (Find cases Actively, Separate safely and Treat effectively) is an intensified, refocused approach to reduce TB (including DR-TB) transmission in health-care facilities (Figure 1). FAST is based on two key principles: 1) rapid molecular tests such as Xpert or LPAs enable prompt diagnosis of TB, including DR-TB, and 2) effective treatment renders patients non-infectious well before sputum smears convert to negative⁵⁸. Evaluation of FAST has revealed high rates of MDR-TB in patients with a history of previously treated TB⁵⁹ that are consistent with other studies^{60, 61}, thereby raising questions about enhanced screening and follow-up of patients with a history of previous TB.

Intense transmission of DR-TB, in prisons is well documented.^{62, 63} However, these congregate settings are a challenge for active case finding approaches due to the high inmate turnover, crowded living conditions and the marginalized nature of the population at risk. Evidence of the impact in reducing prison transmission through active case finding interventions has been mixed. Active case finding implemented at Dhaka Central Jail in Bangladesh led to a decline in the overall number of TB cases and clustered cases, with 2% of the isolates from this study being confirmed as MDR-TB⁶⁴. In Brazilian prisons, however, large-scale active case finding using a symptom-based screen, tuberculin skin test, sputum smear microscopy and mycobacterial culture led to early detection of pulmonary TB but did not reduce the risk of subsequent disease, probably due to the force of infection⁶⁵. More research on implementation of active case finding in prisons and other high-risk congregate settings, such as mines and homeless shelters, is desperately needed.

Mitigating transmission risk in patients with refractory or programmatically incurable drug-resistant TB

Treatment success rates for MDR-TB are currently around 50%, decreasing to approximately 20% for patients with XDR-TB¹. Although a newer regimen consisting of BDQ, linezolid and pretomanid studied in patients with XDR-TB enrolled in the NIX-TB trial has demonstrated excellent preliminary results, with 100% culture conversion at 4 months in the 57/61 patients who survived and only one reported microbiological relapse⁶⁶, there are reports of emerging resistance to the new drugs BDQ and DLM.⁶⁷ It is to be hoped that the numbers of refractory or incurable DR-TB patients will diminish with improved access to DST-guided treatment provided as part of high-quality systems of care.

However, in the meantime, addressing ongoing transmission from these patients remains an important issue. Masks on patients have been shown to be approximately 50% effective in stopping transmission⁶⁸. A novel approach being evaluated as a measure to reduce infectiousness and transmission from patients with incurable TB involves the administration of inhaled antibiotic treatment, such as dry-powder colistin, which is used for the treatment of multidrug-resistant organisms in patients with other structural lung diseases, such as cystic fibrosis⁶⁹.

Adjunctive environmental approaches for the prevention of TB transmission focused on congregate settings

The impact of treatment on transmission relies on prompt diagnosis and treatment, but transmission occurs in indoor environments, before patients are diagnosed and can be treated. A review of WHO 2016 country data indicated that the proportion of new cases of MDR-TB in Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Ukraine, and Uzbekistan were respectively 38, 26, 27, 26, 27, 22, 27, and 24%. Those data were in contrast to most of the remaining top 30 MDR-TB countries, which reported new MDR-TB cases lower than that of China (7.1%)¹. These are not low-income countries nor are they settings of high HIV prevalence. However, most of these countries practice prolonged and repeated hospitalization for TB, particularly DR-TB. In addition to active case finding, using TB molecular diagnostic tools in health care facilities, as described previously,¹⁵ and shifting to predominantly ambulatory or community-based anti-TB treatment, and using environmental interventions to decrease TB (including DR-TB transmission) could be particularly important in these countries, where the cold climate limits ventilation in congregate settings, thereby amplifying transmission.

Environmental controls, such as natural ventilation or upper room germicidal ultraviolet air disinfection (GUV) could be applied as adjunctive TB-IC measures in some congregate settings, although these are typically less applicable to the household setting⁷⁰. Among environmental approaches to TB transmission control, natural ventilation and upper room GUV are the most cost-effective choices⁷¹. Mechanical ventilation can be used in settings with sufficient resources but requires significant maintenance. While highly cost effective, natural ventilation depends on appropriate building design and pressure or temperature differences causing warm air to rise, and is highly reliant on local climate conditions. Ventilation estimates are typically performed (albeit, uncommonly) using labor-intensive

carbon dioxide decay curves, the accuracy of which has been questioned since they are based on single measurements in time, whereas natural ventilation varies minute to minute⁷². For natural ventilation to remain effective, if conditions are favorable, windows should be open at night and in all seasons. However, windows are often closed for security reasons, due to cold, or to keep out vermin. In addition, in the context of global climate change, extreme temperatures are increasingly common. Natural ventilation provides little relief against extreme heat and high humidity, and is increasingly being replaced by split-system (ductless) air conditioning units, which provide cooling but no air exchange, and importantly, require a window to be closed for efficient cooling, which favors transmission of TB (or other airborne infection)⁷³.

GUV air disinfection is among the most well-studied and cost-effective environmental interventions to reduce TB transmission^{72, 74}. Fixtures containing germicidal lamps of wavelength 254-nm are mounted on walls or ceilings in the upper room, above the heads of occupants, and, with appropriate air mixing fans, can provide an estimated 80% reduction in TB transmission⁷⁵. Wide application of GUV could be a particularly useful adjunctive TB transmission control approach in Eastern European or Central Asian countries, with little potential for natural ventilation, prolonged hospitalization, and a resulting high percentage of transmitted new MDR-TB cases.

The main challenges facing GUV involve implementation barriers that include a lack of guidelines, gaps in knowledge and necessary technical support, and ensuring high-quality, low-cost, locally produced fixtures. Additional technology innovation is being explored, for example, a combination of split-system air-conditioning units with upper room GUV air disinfection systems and use of LED UV technology. These barriers are being overcome through work in countries such as India and South Africa, funded by partners including the WHO, the End TB Transmission Initiative at the STOP TB Partnership, Centers for Control and Prevention, and the US Agency for International Development.

Conclusions

Although we focused on various aspects of transmission that are specific to DR-TB, the basic principles of transmission control remain similar for DR-TB and DS-TB. We emphasize the central importance of effective treatment as the primary means of preventing DR-TB transmission, through improved diagnosis, treatment and care of patients with both active and latent MDR-TB (Figure 2). The reduction of TB transmission, including DR-TB, is limited by gaps in our biological understanding of TB, including variability in patient infectiousness and the importance of reinfection, and our ability to identify where transmission is occurring in real-time.

However, much more can be done with existing tools. Barriers to the implementation of rapid molecular diagnostics, which include assessment for drug resistance and early initiation of effective treatment, should be overcome in both community and congregate settings, along with expansion of adjunctive proven technologies such as GUV air disinfection. Improved access to new TB drugs such as BDQ and DLM, as well as further research and development to expand the DR-TB treatment pipeline, are needed urgently to

improve DR-TB treatment outcomes, thereby reducing transmission. Ultimately, robust implementation of a comprehensive package of evidence-based transmission control interventions is critical to reducing MDR-TB incidence and must be a priority at the local and global level.

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Figure 1.
Principles of FAST.

Figure 2. Understanding the role of treatment as prevention to decrease MDR-TB transmission (not to scale).

Circles (not to scale) denoting treatment of active TB (combination of ACF in settings like hospitals and prisons as well as PCF) and treatment of latent TB (contacts as well as other high-risk groups) as well as adjunctive strategies to reduce transmission. MDR-TB=multidrug-resistant tuberculosis; PCF=passive case-finding; ACF=active case-finding; FAST=Find cases Actively, Separate safely and Treat effectively; DST=drug susceptibility testing; TB=tuberculosis; GUV=germicidal ultraviolet air disinfection.